

Hexahydrolupulone is more stable to air than lupulone. Samples of the latter resinify after a few days exposure to the atmosphere at 20–25°, while the hexahydro derivative is stable for several months under these conditions. It is less soluble in organic solvents than lupulone and the sodium salt has a lower solubility in water than the salt of lupulone. Hexahydrolupulone was found to be 6–8 times as active as lupulone on bacteriostatic *in vitro* tube assay to *Streptococcus faecalis* and to *Staphylococcus aureus*.⁴ The compound is inactive in the presence of serum. It is equally as active as lupulone against *Mycobacterium tuberculosis* (H37Rv)⁵ but is inactive to mouse tuberculosis.⁶

Experimental

Lupulone and humulone were isolated from hops by the procedure of Lewis, *et al.*,⁷

Hydrogenation of Lupulone.—Lupulone (m.p. 93–94°) 822 mg. and 250 mg. of palladium-on-charcoal⁸ in 40 ml. of methanol were shaken with hydrogen at atmospheric pressure and 26° for 30 minutes when the absorption of hydrogen became very slow (141.6 cc. (S.T.P.) equivalent to 3.2 moles per mole of lupulone). In a second experiment, 818 mg. of lupulone and 25 mg. of platinum oxide (Adams catalyst) in 40 ml. of methanol were shaken with hydrogen for 45 minutes when reduction was complete. The absorption of hydrogen, 133.5 cc. (S.T.P.) was equivalent to 3.0 moles per mole of lupulone.

On a larger scale 11 g. of lupulone and 3 g. of palladium-on-carbon in 250 ml. of methanol were shaken in a Parr hydrogenation apparatus at 25 lb./sq. in. and 25° for 90 minutes. Removal of catalyst and concentration of the solution *in vacuo* to 50 ml. followed by the addition of 10 ml. of water yielded 8.7 g. (78% yield) of crystalline material, m.p. 134–137°. Recrystallization from hexane and then from methanol at –10° gave hexahydrolupulone, m.p. 140–141°. *Anal.* Calcd. for C₂₈H₄₄O₄: C, 74.24; H, 10.54. Found⁹: C, 73.9; H, 10.4.

When aqueous palladium chloride was used, the results of Wöllmer¹ were completely confirmed. The crude reduction product had an absorption spectrum very similar to that of 3,5-dimethylphloracetophenone¹⁰ and oxidation with air in the presence of lead acetate in methanol yielded tetrahydrohumulone, m.p. 82–83°.

The Hydrogenation of Humulone.—Humulone (1.048 g.) and 600 mg. of palladium-on-carbon in 35 ml. of methanol were shaken with hydrogen for 1 hour when absorption became very slow (hydrogen uptake = 153 cc. (S.T.P.) equivalent to 2.4 moles of hydrogen per mole of humulone). The reduced solution, initially green, rapidly turned red on exposure to air and on concentration *in vacuo* yielded humuloquinone,² m.p. 60–61°, in 5% yield. Platinum oxide gave similar results. The use of smaller quantities of catalyst or termination of the reduction before hydrogen absorption was complete failed to yield tetrahydrohumulone as judged by the absorption spectra of the solutions.

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(4) I am indebted to L. E. Sacks of this Laboratory for these measurements.

(5) These tests were performed by Y. C. Chin and H. H. Anderson of the University of California Medical School, San Francisco, Calif.

(6) Personal communication from F. G. Jones, Eli Lilly Co., Indianapolis, Indiana.

(7) J. C. Lewis, *et al.*, *J. Clin. Invest.*, (Pt. 1), **28**, 916 (1949).

(8) 5% palladium-on-activated charcoal powder, Baker & Co., Newark, N. J. Mention of this product does not imply that it is endorsed or recommended by the Department of Agriculture over others of a similar nature not mentioned.

(9) I am indebted to Miss G. E. Secor for carbon-hydrogen analyses.

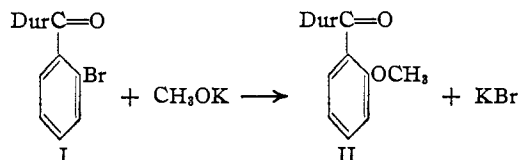
(10) T. W. Campbell and G. M. Coppinger, to be published. Absorption spectra were determined by G. M. Coppinger of this Laboratory.

Methanolysis of Carbonyl-Activated Aryl Bromides

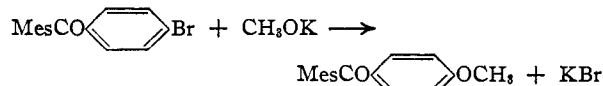
BY REYNOLD C. FUSON AND WILLIAM C. HAMMANN¹

In a search for a convenient method of preparing *o*-methoxybenzoyldurene (II) we were led to attempt alkali-catalyzed methanolysis of the corresponding bromo compound (I). Alcoholysis of aromatic halogen compounds, usually difficult to effect, is known to proceed readily when a nitro group is in an ortho or para position.² However, when a keto group is in an ortho or para position, alcoholysis has not been realized, presumably because of involvement of the carbonyl group.³ It was to be expected that the behavior of ortho and para bromo derivatives of highly hindered ketones would resemble that of the corresponding bromo nitro compound since the ketone group would be protected from attack.

Experiments with *o*-bromobenzoyldurene and with *m*- and *p*-bromobenzoylmesitylene have shown this surmise to be accurate. The *o*-bromo ketone, when heated with a 4.7 *N* potassium methoxide solution for one hour, suffered quantitative displacement of the halogen and gave the corresponding methoxy ketone (II) in a 95% yield.



Under similar conditions *p*-bromobenzoylmesitylene gave *p*-methoxybenzoylmesitylene in a yield of 94%.



m-Bromobenzoylmesitylene reacted sluggishly and in a different manner. A 48-hour period of heating with a 6.0 *N* solution of potassium methoxide sufficed to remove 78% of the bromine, the product being benzoylmesitylene. By contrast, *o*-bromobenzophenone reacted with a 5.3 *N* potassium methoxide solution to yield a mixture containing benzophenone and probably benzohydrol. At the reflux temperature a vigorous reaction took place, and at the end of a 30-minute period of heating, 97% of the bromine had been displaced.

It is known that 4-chloro- and 4-bromobenzophenone react slowly with 3.6 molal ethanolic potassium hydroxide without loss of halogen to yield the corresponding benzohydrol, while 2,4,6-tribromobenzophenone yields 4-bromobenzohydrol.³

Thus it appears that the facility with which methanolysis of *o*- and *p*-bromo hindered benzophenones occurs in the presence of potassium methoxide does not extend to the corresponding meta derivatives or to unhindered bromobenzophenones.

(1) Rohm and Haas Fellow, 1950–1951.

(2) See L. C. Raiford and J. C. Colbert, *THIS JOURNAL*, **48**, 2652 (1926).

(3) M. P. J. Montagne, *Rec. trav. chim.*, **27**, 327 (1908).

Experimental⁴

***o*-Bromobenzoyldurene.**—A mixture of 1.02 g. of *o*-bromobenzoyldurene and 5 ml. of 4.7 *N* potassium methoxide was heated under reflux for one hour. The rate of precipitation of potassium bromide indicated that reaction was rapid and was complete at the end of 15 minutes. The reaction mixture was cooled and diluted with 30 ml. of water. The crude *o*-methoxybenzoyldurene, isolated by filtration, weighed 0.81 g. (95%) and melted at 122–125°. After two recrystallizations from ethanol it melted at 125–126°.

*Anal.*⁵ Calcd. for C₁₃H₂₀O₂: C, 80.56; H, 7.51. Found: C, 80.60; H, 7.70.

Acidification of the filtrate with 3 ml. of glacial acetic acid precipitated 0.023 g. of a compound melting at 93–96°. A mixture with an authentic specimen of *o*-hydroxybenzoyldurene melted at 94–97°.

Volumetric determination of bromide ion showed that 99.1% of the bromine in the original sample had been displaced. Similarly it was found that, when 1.08 g. of *o*-bromobenzoyldurene was heated for five hours with a 2.3 *N* solution of potassium methoxide only 16% of the halogen was displaced.

When a mixture of 110 g. of *o*-bromobenzoyldurene, 152 g. of solid sodium methoxide and 460 ml. of methanol was heated under reflux, *o*-methoxybenzoyldurene was obtained in an 80% yield.

Heating 3.0 g. of the methoxybenzoyldurene with a solution of 8 ml. of glacial acetic acid and 6 ml. of 48% hydrobromic acid under reflux for two hours caused the separation of an oil, which crystallized on cooling.⁶ When the mixture was poured into 100 ml. of water, 2.8 g. (97%) of a white solid was isolated. After recrystallization from petroleum ether (b.p. 45–60°) it melted at 100–101.5°. A mixture with an authentic specimen of *o*-hydroxybenzoyldurene melted at 100–101°. The infrared spectra of the two samples are identical, and the absorption band at 1624 cm.⁻¹ indicates that the molecule is strongly hydrogen-bonded.

o-Bromobenzoyldurene was prepared in a yield of 75% by slowly adding a solution of 16 g. (0.12 mole) of durene in 40 ml. of carbon disulfide to a mixture of 22 g. (0.10 mole) of *o*-bromobenzoyl chloride, 4.6 g. (0.11 mole) of aluminum chloride and 50 ml. of carbon disulfide and stirring at room temperature for four hours. After recrystallization from ethanol the product melted at 134–135°.

Anal. Calcd. for C₁₇H₁₇OBr: C, 64.36; H, 5.40. Found: C, 64.55; H, 5.46.

o-Hydroxybenzoyldurene was prepared in a yield of 48% by a method similar to that used for the preparation of *o*-hydroxybenzophenone.⁷ A solution of 10 g. (0.06 mole) of *o*-methoxybenzoyl chloride in 40 ml. of carbon disulfide was slowly added to a mixture of 9.4 g. (0.07 mole) of durene, 9.3 g. (0.07 mole) of aluminum chloride and 40 ml. of carbon disulfide. After being stirred at room temperature for five hours, the reaction mixture was decomposed with dilute hydrochloric acid and the product isolated in the usual manner. After several recrystallizations from aqueous ethanol it melted at 101–102°.

Anal. Calcd. for C₁₇H₁₅O₂: C, 80.28; H, 7.13. Found: C, 80.06; H, 7.33.

***p*-Bromobenzoylmesitylene.**—By a treatment similar to that described for *o*-bromobenzoyldurene, 1.01 g. of *p*-bromobenzoylmesitylene was converted in 94% yield to a solid, which after several recrystallizations from ethanol melted at 76.5–77°. *p*-Methoxybenzoylmesitylene has been reported to melt at 78°.⁸

Titration of the bromide ion in the filtrate showed that 92% of the bromine in the bromo ketone had been displaced.

***m*-Bromobenzoylmesitylene.**—A mixture of 15 g. of *m*-bromobenzoylmesitylene, 0.3 g. of powdered copper and 75 ml. of 6 *N* potassium methoxide solution was heated under reflux for 48 hours. The product was a yellow, viscous oil which distilled at 120–122° (0.5 mm.). The infrared spectrum was identical with that of benzoylmesitylene.⁹

(4) All melting points are corrected.

(5) The microanalyses were performed by Miss Emily Davis, Miss Rachel Kopel and Mrs. Jean Fortney.

(6) R. Stoermer, *Ber.*, **41**, 321 (1908).

(7) F. Ullmann and I. Goldberg, *ibid.*, **36**, 2811 (1902).

(8) R. C. Fuson and R. Gaertner, *J. Org. Chem.*, **13**, 496 (1948).

(9) The infrared spectra were determined and interpreted by Miss Elizabeth Petersen.

Seeding with crystals of this ketone (m.p. 35°) caused crystallization. The solid so obtained melted at 29–30°.

A nitro derivative was prepared by treating 1 g. of the product with a mixture of concentrated sulfuric acid and fuming nitric acid at 0°. It melted at 202–204°, which is the melting point reported for a trinitrobenzoylmesitylene.¹⁰

Titration of the filtrate showed that 78% of the bromine had been displaced. In subsequent experiments, carried out under varying conditions, the amount of displacement varied from 53 to 95%. The use of powdered copper appeared to promote the conversion slightly.

***o*-Bromobenzophenone.**—A mixture of 10 g. of *o*-bromobenzophenone and 40 ml. of 5.3 *N* potassium methoxide was heated to boiling, whereupon a vigorous reaction took place with the formation of a heavy precipitate. After the reaction had moderated, the mixture was warmed gently for 30 minutes. Addition of 100 ml. of water to the cold reaction mixture caused the solid to dissolve and precipitated an oil, which distilled at 116–118° (1 mm.). The infrared spectrum indicated the presence of a ketone and a carbinol. A semicarbazone after two recrystallizations from ethanol and water had a melting point of 163–164°, which corresponds to the melting point of 164° reported for benzophenone semicarbazone.

Anal. Calcd. for C₁₄H₁₃N₃O: C, 70.27; H, 5.48; N, 17.56. Found: C, 70.06; H, 5.31; N, 17.51.

A 2,4-dinitrophenylhydrazone, prepared in 72% yield, melted at 239–240°. The reported melting point of the 2,4-dinitrophenylhydrazone of benzophenone is 239°. Seeding with crystals of benzophenone caused the oil to crystallize; m.p. 44–46°. The product is a mixture of 75% benzophenone probably accompanied by benzohydrol. Titration of the aqueous solution from the reaction showed that 97% of the bromine had been displaced.

(10) R. C. Fuson and M. D. Armstrong, *THIS JOURNAL*, **63**, 2652 (1941).

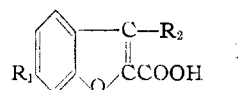
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Basic Derivatives of Coumarilic Acids

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Previous investigations of basic esters and amides derived from the coumarin nucleus¹ have been extended in the present work to similar derivatives of certain coumarilic acids, I. Since a coumarilic



acid contains the carbon chain of cinnamic acid, it was expected that in analogy with, *e. g.*, Apothesine, local anesthetic activity would be found in this series. This expectation was fully realized. The simple basic esters of coumarilic acid were very active, both topically and by infiltration. However, the compounds proved to be very irritating, and the series was not extended to more than a few examples.

Experimental²

Coumarilic Acids.—These compounds were prepared by the usual method³ from the corresponding coumarin intermediates. From 4,7-dimethylcoumarin was obtained an 83% yield of 3,6-dimethylcoumarilic acid, m.p. 214–216° (dec.) (lit.⁴ m.p. *ca.* 212° (dec.)). The reaction between

(1) Clinton and Laskowski, *THIS JOURNAL*, **71**, 3602 (1949); Laskowski and Clinton, *ibid.*, **72**, 3987 (1950).

(2) All melting points are corrected. The authors are indebted to Mr. Morris E. Auerbach and staff for the analyses.

(3) Cf. Fuson, Kneisley and Kaiser, *Org. Syntheses*, **24**, 33 (1944).

(4) Fries and Pickewirth, *Ann.*, **362**, 50 (1908); Dey, *J. Chem. Soc.*, **107**, 1647 (1915).